Pump the organ: procurement and resuscitation technologies beyond static cold storage

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The current section of organ preservation and procurement focuses on dynamic organ preservation and resuscitation technologies in solid organ transplantation. The main goal of this section was to highlight the latest developments in machine perfusion technologies in cardiothoracic and abdominal organ transplantation. *Current Opinion in Organ Transplantation* is delighted to present top reviews from leading international expert groups, including groups from the United States [1], the Netherlands [2], Great Britain [3], Switzerland [4], Canada [5,6], Spain [7], and Australia [8].

Organ perfusion has been already approached in the beginning of the last century by French surgeon Axel Carrel who became Nobel laureate in 1912 for his contribution in vascular suture techniques and transplantation. At this time, Carrel designated his work to the idea of maintaining organs viable outside the body. After he met engineer Charles Lindbergh [9], who is known for the first transatlantic flight in 1927, both scientists developed the perfusion pump, which was a complex glass apparatus at this time. Using this technology at normothermic conditions, Carrel and Lindbergh [10] were able to maintain contractions of cat hearts for a period of 12 h [11]. These groundbreaking achievements represented the birth of organ perfusion and appeared to be so spectacular at this time that both scientists appeared on the cover page of the *TIME* magazine in 1938 [12].

The further development of perfusion systems for the clinical use in organ transplantation was marginally driven during the last quarter of the last century because of the availability of efficient procurement solutions for static cold storage preservation as described by the Milwaukee group in this section [1]. Static cold storage is an easy applicable preservation method and remained the standard preservation over a long period. The extreme shortage of donor organs and the urgent need to expand the donor pool by using marginal and donation after cardiac death (DCD) organs resulted in a clinical revival of dynamic preservation methods during the last decade [13]. This has been also mirrored by the increasing annual number of publications on this topic (Fig. 1).

Common goals of machine perfusion as reported by almost all groups in the present section are: expansion of the donor pool by using marginal and DCD organs, mitigation of ischemia-reperfusion injury, resuscitation of marginal and DCD organs, well tolerated prolongation of 'out of the body' time, and rapid assessment of organ function before implantation to improve graft selection. The question whether organs should be perfused cold or warm follows the two main perfusion strategies of hypothermic versus normothermic perfusion. The physiologic aspects of temperature-regulated perfusion have been discussed in detail especially for kidney and liver by Zimmermann *et al.* [1].

Currently, machine perfusion in kidney transplantation has achieved the most clinical advancement. The current state of hypothermic and normothermic machine perfusion in kidney transplantation has been described in this section by expert groups from Groningen [2] and Cambridge [3]. Although both strategies have been successfully evaluated in clinical kidney transplantation, only hypothermic machine perfusion reached the stage of completing a randomized controlled trial. The Groningen group reported that '...hypothermic machine perfusion has been proven effective for all types of deceased donor kidneys; its beneficial effect was outstanding for extended criteria donor (ECD) grafts' [2]. Hypothermic and normothermic machine perfusion has been evaluated in liver transplantation as well. The concept of hypothermic oxygenated perfusion as performed by Zurich group [4] appears an attractive strategy to improve organ

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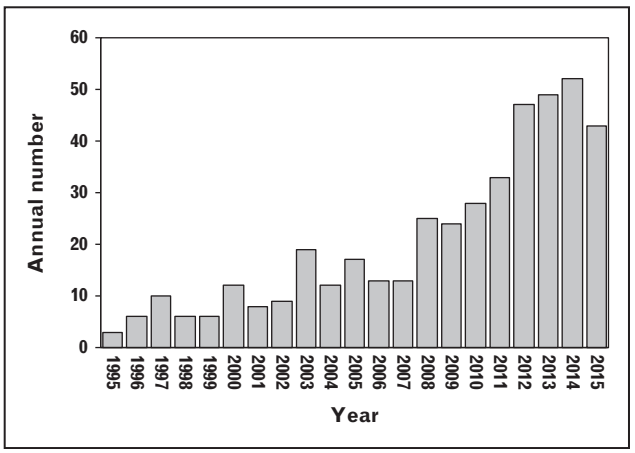

FIGURE 1. Annual number of publications on machine perfusion. For the period 1995–2015, in total 435 publications were retrieved from PubMed on 1 April 2016 using search [machine perfusion] AND [organ transplantation].

quality and posttransplant outcome of donation after brain death (DBD) and DCD livers. This concept relies on a short endischemic hypothermic oxygenated perfusion for 1–2 h before implantation. But also normothermic and subnormothermic machine perfusion appears to be an attractive strategy in liver transplantation as reported by the Toronto group in this section [5]. A recently published phase 1 trial from the Oxford group has demonstrated safety and feasibility of this technology [14]. Whether normothermic or hypothermic oxygenated perfusion is superior in kidney and liver transplantation remains to be demonstrated in the future. Currently, there are ongoing randomized controlled trials investigating both concepts of hypothermic and normothermic machine perfusion in liver transplantation.

The role of oxygen supply during hypothermic perfusion has been addressed by various experimental and clinical studies. Although a direct comparison is lacking, De Deken *et al.* [2] and Schlegel *et al.* [4] stated that experimental and clinical studies in kidney and liver transplantation suggest that hypothermic perfusion with oxygen supply appears to be superior to hypothermic perfusion without oxygen.

Another important concept to procure controlled or uncontrolled abdominal DCD organs is advocated by the Barcelona group in this section, called abdominal regional perfusion [7]. This perfusion technique applies to the time before organ retrieval and has been clinically evaluated under hypothermic and normothermic conditions. The authors of this review report that normothermic abdominal regional perfusion is preferred when retrieval of more than one organ system (e.g., kidneys and liver) is targeted. By using this technique, even uncontrolled abdominal DCD organs can be successfully resuscitated that might otherwise not be considered for transplantation.

The beneficial effects of machine perfusion in abdominal organ transplantation have been also observed for cardiothoracic organs as reported by Cypel *et al.* [6] and McDonald *et al.* [8] in this section. Organs with extended criteria or from DCD donors appear to be associated with the highest benefit. Although hypothermic machine perfusion has been evaluated in cardiac transplantation, McDonald *et al.* [8] consider normothermic machine perfusion as the '...most promising approach to the successful recovery and transplantation of hearts from human DCD donors...'. Especially organs, which tolerate less longer periods of cold ischemia such as the heart, machine perfusion may offer an effective strategy that can safely prolong the 'out of the body' time.

In summary, all reviews of the present section on dynamic organ preservation reflect growing evidence that machine perfusion of abdominal and cardiothoracic organs is associated with beneficial effects especially for ECD and DCD organs. By applying this technology, organs can be successfully resuscitated that might be otherwise discarded. The current and future application of perfusion systems offers a promising strategy to expand the donor pool, a strategy that can save many lives on the waiting list.

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Conflicts of interest

There are no conflicts of interest.

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